# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/821,203 | 04/09/2004 | David Sidransky | 001107.00463 | 9884 |

22907 7590 01/13/2006

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

| EXAMINER | |
|---|---|
| JOYCE, CATHERINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/821,203 | SIDRANSKY ET AL. | |
| | Examiner | Art Unit | |
| | Catherine M. Joyce | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-24 are pending, and claims 15-24 are withdrawn from consideration as being drawn to a non-elected invention.

2. Claims 1-14 are under examination.

3. Applicant's election of Group II, claims 11-14, in the reply filed on November 21, 2005 is acknowledged. Because Applicant applicant did not distinctly and specifically point out supposed errors in the restriction requirement, the election is treated as an election without traverse. Claims 1-10 have also been rejoined for examination.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are objected to as being indefinite in the use of the designation BRAF as the sole means for identifying the claimed gene. The use of laboratory designations only to identify a particular gene renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct genes. The amendment of the claims to recite a specific sequence identifier for the BRAF gene is suggested.

The claims are also objected to as being indefinite in the use of an undefined reference point. The claim recites the phrase nucleotide 1796 of BRAF but it is not

clear which particular BRAF gene is intended. The amendment of the claims to recite a specific sequence identifier for the BRAF gene is suggested.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for distinguishing malignant from benign thyroid samples, comprising determining the presence of a T to A transversion at nucleotide 1796 of BRAF in a blood sample (claim 10) and to methods for detecting a mutation at nucleotide 1796 of BRAF comprising amplifying all or part of exon 15 of BRAF from a test sample, wherein the part comprises at least nucleotides 1792 to 1799 of BRAF, and digesting the amplified products with restriction endonuclease TspRI (claims 11-14).

The specification discloses methods for distinguishing malignant from benign thyroid samples wherein the presence of a T to A transversion at nucleotide 1796 of BRAF indicates a malignant thyroid neoplasm and the absence of the transversion indicates a benign neoplasm in the sample (paragraph 08). The specification also discloses that BRAF is frequently mutated in a variety of human tumors, especially malignant melanoma and colon carcinoma, and that the most common reported mutation is a missense T to A transversion at nucleotide 1796 that is observed in 80% of malignant melanoma tumors. The specification also teaches that the BRAF T to A transversion at nucleotide 1796 was identified in head and neck cancers and in lung cancers (paragraph 29).

One cannot extrapolate the teaching of the specification to the enablement of the claims because one cannot determine that the claimed methods would be useful in distinguishing benign thyroid neoplasms from malignant thyroid neoplasms. As disclosed in the specification and as disclosed in Davies et al. (2002, Nature 417:953-954) (Table 1), a missense T to A transversion at nucleotide 1796 is observed in a high percentage of malignant melanomas and in a significant percentage of colon carcinomas. Further, as disclosed in the specification, the transversion is observed in head and neck cancers and in lung cancers. Thus, determining the presence of a T to A transversion at nucleotide 1796 of BRAF in a blood sample of a human would not allow one skill in the art to determine that a malignant thyroid neoplasm is indicated because the presence of the transversion may indicate the presence of melanoma cells,

colon cancer cells, head and neck cancer cells, or lung cancer cells in the blood. Further, as disclosed in Wolf et al. (2002, Hautarzt. 53(5):332-2) malignant melanoma metastasizes to the thyroid (abstract). Thus, determining the presence of a T to A transversion at nucleotide 1796 of BRAF in a tissue sample from a thyroid or in a fine needle aspirate of a thyroid would not allow one of skill in the art to determine that a malignant thyroid neoplasm is indicated because the presence of the transversion may indicate the presence of metastasized melanoma in the thyroid sample. Thus, it cannot be predicted, and one of skill in the art would not expect, that the invention will function as claimed.

8. Further, if the rejection of claims 11-14 above is overcome, the claims would still be rejected under under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a mutation at nucleotide 1796 of BRAF, wherein the mutation is a T to A transversion, is not enabling for a method of detecting a mutation at nucleotide 1796 of BRAF.

The specification teaches that a T to A transversion at nucleotide 1796 of BRAF is associated with papillary thryroid cancer, melanoma, malignant melanoma and colon carcinoma. The specification does not specifically teach that any other mutation at nucleotide 1796 of BRAF is associated with cancer and therefore, one of skill in the art could not predict and would not expect that methods of detecting other types of mutations would be useful in the art. Therefore, the specification does not teach how to make and use the invention wherein the mutation at 1796 at BRAF is any other mutation other than a T to A transversion.

9. Claims 11-14 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to a method of detecting a mutation at nucleotide 1796 of BRAF.

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of "a method of detecting a mutation at nucleotide 1796 of BRAF per Lilly by structurally describing a representative number of species of mutations a nucleotide 1796 of BRAF or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe mutations at nucleotide 1796 of BRAF in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any mutation, nor does the specification provide any partial structure of such mutations, nor any physical or chemical characteristics of such mutations, nor any functional characteristics coupled with a known or disclosed correlation between structure and function, other than the T to A transversion at nucleotide 1796. Although the specification discloses a single mutation

at polynucleotide 1796, this does not provide a description of the detection of any mutation at nucleotide 1796 using the claimed methods that would satisfy the standard set out in Enzo.

The specification also fails to describe the mutations at polynucleotide 1796 by the test set out in Lilly. The specification describes only a single mutation a polynucleotide 1796 that is a T to A transversion. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the claimed method for detecting a mutation at polynucleotide 1796 of BRAF

10. No claims are allowed.

## Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Catherine Joyce
Examiner
Art Unit 1642